one of E, D and F must be nitrogen or substituted nitrogen, and only one of E, D and F can be nitrogen or substituted nitrogen;

Z is NH, oxygen, sulfur, -N(C_1-C_4 alkyl), -NC(=O)(C_1-C_2 alkyl) NC(-O)O(C_1-C_2 alkyl or CR^{13} R^{14} wherein R^{13} and R^{14} are independently selected from hydrogen, trifluoromethyl and methyl with the exception that one of R^{13} and R^{14} can be cyano;

or a pharmaceutically acceptable salt of such compound.

REMARKS

The amended claim is set out in the Appendix showing the amendments made.

Claims 18 and 25 have been amended to meet most of the points raised in the final rejection. In particular,

1) the definition of the $CR^1R^2R^3$ has been amended so as to conform with that of the claims as originally filed as carbocyclic with the possibility that when the ring has from 5 to 8 members on or two of the ring carbons may be independently replaced by oxygen sulfur of NZ^3.

2) The "alkylthio" language has been deleted.

3) The examiner's proposed wording for the provisoes in the definition of F has, except for an obvious typographical error, been adopted in both of claims 18 and 25.

It is, however, respectfully submitted that the definition of R^4 as CF_3 should be acceptable. The original definition in claim 1 included C_1-C_6 alkyl ... optionally substituted with one or two substituents independently selected from ... fluorine.... . Page 9 refers to R^4 as trifluoromethyl but only in juxtaposition to other groups having certain particular definitions. The applicants have previously argued that each of these groups of definitions should be taken separately. The examiner argues that they are cumulative. Either way, the passage on page 9 shows that CF_3 was under some circumstances intended to fall within the broad definition of R^4. Once this is established, the

question surely is whether it is more likely that it was intended to be present in only limited situations or generally. There seems to be no logical reason why one should opt for the more restricted view and we submit that one skilled in the art reading the original disclosure would have concluded that the definition of R^4 should be read so as to include CF_3.

In view of the foregoing it is believed that this application is now in order for allowance. An early action to this end is respectfully solicited. If the Examiner believes it would be useful to discuss this matter either personally or in a telephone interview, he is requested to let us know so that this can be arranged.

Respectfully submitted,

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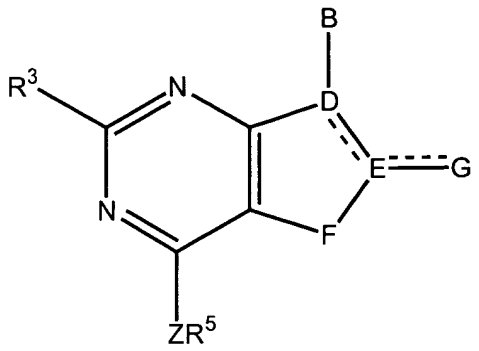
Appendix - Amended claims showing changes

18. A compound of the formula



wherein the dashed lines represent optional double bonds;

B is $-NR^1R^2$, $-CR^1R^2R^{10}$, $-C(=CR^2R^{11})R^1$, $-NHCR^1R^2R^{10}$, $-OCR^1R^2R^{10}$, $-SCR^1R^2R^{10}$, $CR^2R^{10}NHR^1$, $-CR^2R^{10}OR^1$, $-CR^2R^{10}SR^1$ or $-COR^2$;

E is nitrogen, CH or carbon;

D is nitrogen and is single bonded to all atoms to which it is attached, or D is carbon and is double bonded to E, or D is CH and is single bonded to E;

F is CHR^4 or NR^4; provided that **either 1) exactly one of D or E is nitrogen and F is CHR^4, or 2) F is NR^4 and neither D nor E is nitrogen** [at least one of D and E is nitrogen or F is NR^4, and provided that only one of D and E is nitrogen and D and E are not nitrogen when F is NR^4];

G, when single bonded to E is hydrogen, C_1-C_4 alkyl, $-S(C_1$-C_4 alkyl), $-O(C_1$-C_4 alkyl), NH_2, $-NH(C_1$-C_4 alkyl) or $-N(C_1$-C_2 alkyl)(C_1-C_4 alkyl) wherein each of the C_1-C_4 alkyl groups of G may optionally be substituted by one hydroxy, $-O(C_1$-C_2 alkyl) or fluoro group; and G when double bonded to E is oxygen, sulfur or NH; and G, when E is nitrogen and double bonded to D, is absent;

R^1 is hydrogen, C_1-C_6 alkyl optionally substituted with one or two substituents R^8 independently selected from hydroxy, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, CF_3, $-C(=O)O-(C_1$-$C_4)$alkyl, $-OC(=O)(C_1$-$C_4)$alkyl, $OC(=O)N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), $-NHCO(C_1$-C_4 alkyl), $-COOH$, $-COO(C_1$-C_4 alkyl), $-CONH(C_1$-C_4 alkyl), $-CON(C_1$-C_4 alkyl)(C_1-C_2 alkyl), $-S(C_1$-C_4 alkyl), $-CN$, NO_2, $-SO(C_1$-C_4 alkyl), $-SO_2(C_1$-C_4 alkyl), $-SO_2NH(C_1$-C_4 alkyl), $SO_2N(C_1$-C_4 alkyl)(C_1 - C_2 alkyl), wherein a carbon-carbon single bond of each of the C_1-C_4 alkyl groups in the foregoing R^1 groups having at least two carbons may optionally be replaced with a carbon-carbon double or triple bond, and one or two carbon-carbon single bonds of each of the C_1-C_4 alkyl groups in the foregoing R^1 groups having four carbon atoms may optionally be replaced with a carbon-carbon double or triple bond; R^2 is C_1-C_{12} alkyl wherein one carbon-carbon single bond of any said alkyl group having at least two carbons, one or two carbon-carbon single bonds of any alkyl having at least four carbons, and from one to three carbon-carbon single bonds of any said alkyl having at least six carbons may optionally be replaced with a carbon-carbon double or triple bond; or R^2 is aryl or (C_1-C_4 alkylene)aryl, wherein said aryl and the aryl moiety of said

(C_1-C_4 alkylene)aryl is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; or R^2 is C_3-C_8 cycloalkyl or (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl), wherein one or two of the carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl) may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^2 wherein Z^2 is selected from hydrogen, C_1-C_4 alkyl, benzyl and C_1-C_4 alkanoyl, and wherein each of the foregoing R^2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, hydroxy and C_1-C_4 alkyl, or with one substitutent selected from bromo, iodo, C_1-C_6 alkoxy, -OC(=O)(C_1-C_6 alkyl), OC(=O)N (C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1 -C_6 alkyl), amino, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)-CO-(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), CO N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SH, -CN, -NO_2, -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl) and -SO_2N (C_1-C_4 alkyl)(C_1-C_2 alkyl);

-NR^1R^2 or -$CR^1R^2R^{10}$ may form a 3 to 8 membered ring, **that in the case of -$CR^1R^2R^{10}$ is carbocyclic, said ring** consisting of single bonds, wherein, **when said ring has from 5 to 8 members,** one or two of the ring carbon atoms of such a 5 to 8 membered ring may optionally and independently br replaced by an oxygen or sulfur atom or by NZ^3 wherein Z^3 is hydrogen, C_1-C_4 alkyl, benzyl and C_1-C_4 alkanoyl, and wherein from one to three of the single bonds of such a 3 to 8 membered ring that are carbon-carbon or carbon-nitrogen single bonds may each optionally be replaced by a double bond;

R^3 is hydrogen, C_1-C_4 alkyl, O(C_1-C_4 alkyl), chloro, fluoro, bromo, iodo, -CN, -S(C_1-C_4 alkyl) or -SO_2(C_1-C_4 alkyl) wherein each of the (C_1-C_4 alkyl) moieties in the foregoing R^3 groups may optionally be substitued with one substituent R^9 selected from hydroxy, fluoro and (C_1-C_2 alkoxy);

each of R^4 is, independently hydrogen, (C_1-C_6 alkyl), fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, cyano, amino, nitro, -O(C_1-C_4 alkyl), N (C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -C(=O)H or C(=O)O (C_1-C_4 alkyl), wherein one or two of the carbon-carbon single bonds in each of the (C_1-C_6 alkyl) and (C_1-C_4 alkyl) moieties in the foregoing R^4 groups may optionally be replaced with a carbon-carbon double or triple bond and wherein each of said (C_1-C_6 alkyl) and (C_1-C_4 alkyl) moieties may optionally be substitued with one or two substituents independently selected from hydroxy, amino, C_1-C_3 alkoxy, dimethylamino, methylamino, ethylamino, -NHC(=O)CH_3, fluoro, chloro, [~~C_1-C_3 alkylthio~~], -CN, -COOH, -C(=O)O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl) and NO_2;

R^5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, benzoxazolyl or C_3-C_8 cycloalkyl wherein one or two of the carbon atoms of said cycloalkyl rings that contain at least 5 ring members may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^4 wherein N^4 is hydrogen, C_1-C_4 is alkyl or benzyl; and wherein each of the foregoing R^5 groups is substituted with from one to four substituents wherein one to three of said substituents may be selected, independently, from chloro, C_1-C_6 alkyl and -O(C_1-C_6 alkyl) and one of said substituents may be selected from bromo, iodo, formyl, -CN, -CF_3, -NO_2, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_6 alkyl), -C(=O)O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl), -COOH, -SO_2NH(C_1-C_4 alkyl), -SO_2N (C_1-C_2 alkyl) (C_1-C_4 alkyl), -SO_2NH_2, $NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and -SO_2 (C_1-C_6 alkyl), and wherein each of the C_1-C_4 alkyl and C_1-C_6 alkyl, moieties in the

foregoing R^5 groups may optionally be substituted with one or two substituents independently selected from fluoro, hydroxy, amino, methylamino, dimethylamino and acetyl; and furthermore wherein when R^5 is phenyl or pyridyl substituted with three substituents, said substituents can further be selected from (C_1-C_4 alkyl)O(C_1-C_4 alkyl), OCF_3, and fluoro, and one carbon-carbon single bond of each (C_1-C_4) alkyl group of said substituents having between two and four carbon atoms may be optionally replaced with a carbon-carbon double or triple bond; or R^5 is pyrimidyl substituted by three substituents independently selected from C_1-C_4 alkyl, -O(C_1-C_4 alkyl), CF_3, OCF_3, -CHO, (C_1-C_4 alkyl)-OH, CN, Cl, F, Br, I and NO_2, wherein a carbon-carbon single bond of said (C_1-C_4) alkyl groups having been two and four carbon atoms may optionally be replaced by a carbon-carbon double or triple bond;

R^7 is hydrogen, C_1-C_4 alkyl, halo, cyano, hydroxy, -O(C_1-C_4 alkyl) -C(=O)(C_1-C_4 alkyl), -C(=O)O(C_1-C_4 alkyl), $-OCF_3$, $-CF_3$, $-CH_2$-OH, $-CH_2O(C_1$-C_4 alkyl);

R^{10} is hydrogen, hydroxy, methoxy or fluoro;

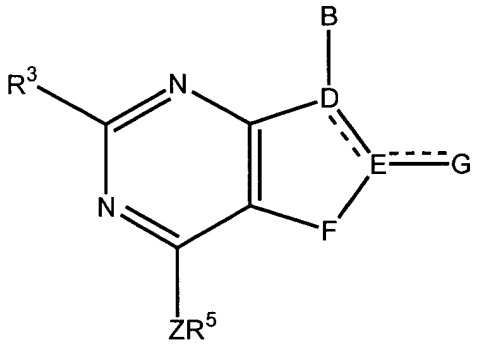
R^{11} is hydrogen or C_1-C_4 alkyl; and

with the proviso that: (a) when R^4 is attached to nitrogen, it not halo, cyano or nitro; and (b) one of E, D and F must be nitrogen or substituted nitrogen, and only one of E, D and F can be nitrogen or substituted nitrogen;

Z is NH, oxygen, sulfur, -N(C_1-C_4 alkyl), -NC(=O)(C_1-C_2 alkyl) NC(-O)O(C_1-C_2 alkyl or CR^{13} R^{14} wherein R^{13} and R^{14} are independently selected from hydrogen, trifluoromethyl and methyl with the exception that one of R^{13} and R^{14} can be cyano;

or a pharmaceutically acceptable salt of such compound.

25. A compound of the formula



wherein the dashed lines represent optional double bonds;

B is $-NR^1R^2$, $-CR^1R^2R^{10}$, $-C(=CR^2R^{11})R^1$, $-NHCR^1R^2R^{10}$, $-OCR^1R^2R^{10}$, $-SCR^1R^2R^{10}$, $CR^2R^{10}NHR^1$, $-CR^2R^{10}OR^1$, $-CR^2R^{10}SR^1$ or $-COR^2$;

E is nitrogen, CH or carbon;

D is nitrogen and is single bonded to all atoms to which it is attached, or D is carbon and is double bonded to E, or D is CH and is single bonded to E;

F is CHR^4 or NR^4; provided that **either 1) exactly one of D or E is nitrogen and F is CHR^4 or**

2) F is NR^4 and neither D nor E is nitrogen [~~at least one of D and E is nitrogen or F is NR^4, and provided that only one of D and E is nitrogen and D and E are not nitrogen when F is NR^4~~];

G, when single bonded to E is hydrogen, C_1-C_4 alkyl, -S(C_1-C_4 alkyl), -O(C_1-C_4 alkyl), NH_2, -NH(C_1-C_4 alkyl) or -N (C_1-C_2 alkyl)(C_1-C_4 alkyl) wherein each of the C_1-C_4 alkyl groups of G may optionally be substituted by one hydroxy, -O(C_1-C_2 alkyl) or fluoro group; and G when double bonded to E is oxygen, sulfur or NH; and G, when E is nitrogen and double bonded to D, is absent;

R^1 is hydrogen, C_1-C_6 alkyl optionally substituted with one or two substituents R^8 independently selected from hydroxy, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, CF_3, -C(=O)O-(C_1-C_4)alkyl, -OC(=O)(C_1-C_4)alkyl, OC(=O)N (C_1-C_4 alkyl)(C_1-C_2 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON (C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_4 alkyl), -CN, NO_2, -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1 - C_2 alkyl), wherein a carbon-carbon single bond of each of the C_1-C_4 alkyl groups in the foregoing R^1 groups having at least two carbons may optionally be replaced with a carbon-carbon double or triple bond, and one or two carbon-carbon single bonds of each of the C_1-C_4 alkyl groups in the foregoing R^1 groups having four carbon atoms may optionally be replaced with a carbon-carbon double or triple bond; R^2 is C_1-C_{12} alkyl wherein one carbon-carbon single bond of any said alkyl group having at least two carbons, one or two carbon-carbon single bonds of any alkyl having at least four carbons, and from one to three carbon-carbon single bonds of any said alkyl having at least six carbons may optionally be replaced with a carbon-carbon double or triple bond; or R^2 is aryl or (C_1-C_4 alkylene)aryl, wherein said aryl and the aryl moiety of said (C_1-C_4 alkylene)aryl is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; or R^2 is C_3-C_8 cycloalkyl or (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl), wherein one or two of the carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said (C_1-C_6 alkylene)(C_3-C_8 cycloalkyl) may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^2 wherein Z^2 is selected from hydrogen, C_1-C_4 alkyl, benzyl and C_1-C_4 alkanoyl, and wherein each of the foregoing R^2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, hydroxy and C_1-C_4 alkyl, or with one substitutent selected from bromo, iodo, C_1-C_6 alkoxy, -OC(=O)(C_1-C_6 alkyl), OC(=O)N (C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1 -C_6 alkyl), amino, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -N(C_1-C_4 alkyl)-CO-(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COOH, -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), CO N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SH, -CN, -NO_2, -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl) and -SO_2N (C_1-C_4 alkyl)(C_1-C_2 alkyl);

-NR^1R^2 or -$CR^1R^2R^{10}$ may form a 3 to 8 membered ring, **that in the case of -$CR^1R^2R^{10}$ is carbocyclic, said ring** consisting of single bonds, wherein, **when said ring has from 5 to 8 members,** one or two of the ring carbon atoms of such a 5 to 8 membered ring may optionally and independently br replaced by an oxygen or sulfur atom or by NZ^3 wherein Z^3 is hydrogen, C_1-C_4 alkyl, benzyl and C_1-C_4 alkanoyl, and wherein from one to three of the single bonds of such a 3 to 8 membered ring that are carbon-carbon or carbon-nitrogen single bonds may each optionally be replaced by a double bond;

R^3 is hydrogen, C_1-C_4 alkyl, O(C_1-C_4 alkyl), chloro, fluoro, bromo, iodo, -CN, -S(C_1-C_4 alkyl) or -SO_2(C_1-C_4 alkyl) wherein each of the (C_1-C_4 alkyl) moieties in the foregoing R^3 groups may optionally be substitued with one substituent R^9 selected from hydroxy, fluoro and (C_1-C_2 alkoxy);

each of R^4 is, independently hydrogen, (C_1-C_6 alkyl), fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, cyano, amino, nitro, -O(C_1-C_4 alkyl), N (C_1-C_4 alkyl)(C_1-C_2 alkyl),

-S(C_1-C_4 alkyl), -SO(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -C(=O)H or C(=O)O (C_1-C_4 alkyl), wherein one or two of the carbon-carbon single bonds in each of the (C_1-C_6 alkyl) and (C_1-C_4 alkyl) moieties in the foregoing R^4 groups may optionally be replaced with a carbon-carbon double or triple bond and wherein each of said (C_1-C_6 alkyl) and (C_1-C_4 alkyl) moieties may optionally be substitued with one or two substituents independently selected from hydroxy, amino, C_1-C_3 alkoxy, dimethylamino, methylamino, ethylamino, -NHC(=O)CH_3, fluoro, chloro, [~~C_1-C_3-alkylthio~~], -CN, -COOH, -C(=O)O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl) and NO_2;

R^5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, benzoxazolyl or C_3-C_8 cycloalkyl wherein one or two of the carbon atoms of said cycloalkyl rings that contain at least 5 ring members may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^4 wherein N^4 is hydrogen, C_1-C_4 is alkyl or benzyl; and wherein each of the foregoing R^5 groups is substituted with from one to four substituents wherein one to three of said substituents may be selected, independently, from chloro, C_1-C_6 alkyl and -O(C_1-C_6 alkyl) and one of said substituents may be selected from bromo, iodo, formyl, -CN, -CF_3, -NO_2, -NH_2, -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_6 alkyl), -C(=O)O(C_1-C_4 alkyl), -C(=O)(C_1-C_4 alkyl),
-COOH, -SO_2NH(C_1-C_4 alkyl), -SO_2N (C_1-C_2 alkyl) (C_1-C_4 alkyl), -SO_2NH_2, NHSO_2(C_1-C_4 alkyl),-S(C_1-C_6 alkyl) and -SO_2 (C_1-C_6 alkyl), and wherein each of the C_1-C_4 alkyl and C_1-C_6 alkyl, moieties in the foregoing R^5 groups may optionally be substituted with one or two substituents independently selected from fluoro, hydroxy, amino, methylamino, dimethylamino and acetyl;

R^7 is hydrogen, C_1-C_4 alkyl, halo, cyano, hydroxy, -O(C_1-C_4 alkyl) -C(=O)(C_1-C_4 alkyl), -C(=O)O(C_1-C_4 alkyl), -OCF_3, -CF_3, -CH_2-OH, -CH_2O(C_1-C_4 alkyl);

R^{10} is hydrogen, hydroxy, methoxy or fluoro;

R^{11} is hydrogen or C_1-C_4 alkyl; and

with the proviso that: (a) when R^4 is attached to nitrogen, it not halo, cyano or nitro; and (b) one of E, D and F must be nitrogen or substituted nitrogen, and only one of E, D and F can be nitrogen or substituted nitrogen;

Z is NH, oxygen, sulfur, -N(C_1-C_4 alkyl), -NC(=O)(C_1-C_2 alkyl) NC(-O)O(C_1-C_2 alkyl or CR^{13} R^{14} wherein R^{13} and R^{14} are independently selected from hydrogen, trifluoromethyl and methyl with the exception that one of R^{13} and R^{14} can be cyano;

or a pharmaceutically acceptable salt of such compound.